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INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 101301-1 WO	<b>FOR FURTHER ACTION</b>		See Form PCT/IPEA/416
International application No. PCT/GB2004/004937	International filing date (day/month/year) 24.11.2004	Priority date (day/month/year) 26.11.2003	
International Patent Classification (IPC) or national classification and IPC C07D403/04, C07D231/56, C07D487/04, A61K31/405, A61P11/06			
Applicant ASTRAZENECA AB et al.			
<p>1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.</p> <p>2. This REPORT consists of a total of 5 sheets, including this cover sheet.</p> <p>3. This report is also accompanied by ANNEXES, comprising:</p> <p>a. <input type="checkbox"/> <i>(sent to the applicant and to the International Bureau) a total of sheets, as follows:</i></p> <p><input type="checkbox"/> sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).</p> <p><input type="checkbox"/> sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.</p> <p>b. <input type="checkbox"/> <i>(sent to the International Bureau only) a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).</i></p> <p>4. This report contains indications relating to the following items:</p> <p><input checked="" type="checkbox"/> Box No. I Basis of the opinion</p> <p><input type="checkbox"/> Box No. II Priority</p> <p><input type="checkbox"/> Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability</p> <p><input type="checkbox"/> Box No. IV Lack of unity of invention</p> <p><input checked="" type="checkbox"/> Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement</p> <p><input type="checkbox"/> Box No. VI Certain documents cited</p> <p><input type="checkbox"/> Box No. VII Certain defects in the international application</p> <p><input type="checkbox"/> Box No. VIII Certain observations on the international application</p>			
Date of submission of the demand 07.06.2005	Date of completion of this report 18.10.2005		
Name and mailing address of the international preliminary examining authority:  European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Lauro, P Telephone No. +49 89 2399- 		

**INTERNATIONAL PRELIMINARY REPORT  
ON PATENTABILITY**International application No.  
PCT/GB2004/004937**Box No. I Basis of the report**

1. With regard to the language, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.
  - This report is based on translations from the original language into the following language, which is the language of a translation furnished for the purposes of:
    - international search (under Rules 12.3 and 23.1(b))
    - publication of the international application (under Rule 12.4)
    - international preliminary examination (under Rules 55.2 and/or 55.3)
2. With regard to the elements\* of the international application, this report is based on (replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report):

**Description, Pages**

1-39 as originally filed

**Claims, Numbers**

1-14 as originally filed

- a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3.  The amendments have resulted in the cancellation of:
  - the description, pages
  - the claims, Nos.
  - the drawings, sheets/figs
  - the sequence listing (specify):
  - any table(s) related to sequence listing (specify):

4.  This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).

- the description, pages
- the claims, Nos.
- the drawings, sheets/figs
- the sequence listing (specify):
- any table(s) related to sequence listing (specify):

\* If item 4 applies, some or all of these sheets may be marked "superseded."

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**INTERNATIONAL PRELIMINARY REPORT  
ON PATENTABILITY**

International application No.  
PCT/GB2004/004937

**Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

**1. Statement**

Novelty (N)	Yes: Claims	
	No: Claims	1-14
Inventive step (IS)	Yes: Claims	
	No: Claims	1-14
Industrial applicability (IA)	Yes: Claims	1-10,13-14
	No: Claims	11-12

**2. Citations and explanations (Rule 70.7):**

**see separate sheet**

**INTERNATIONAL PRELIMINARY  
REPORT ON PATENTABILITY  
(SEPARATE SHEET)**

International application No.

PCT/GB2004/004937

**Re Item V**

1. Reference is made to the following documents:

D1: WO 03/066046 A (ASTRAZENECA AB; BAXTER, ANDREW; STEELE, JOHN; TEAGUE, SIMON) 14 August 2003 (2003-08-14)  
D2: WO 03/066047 A (ASTRAZENECA AB; BAXTER, ANDREW; STEELE, JOHN; TEAGUE, SIMON) 14 August 2003 (2003-08-14)  
D3: EP-A-1 170 594 (PFIZER PRODUCTS INC) 9 January 2002 (2002-01-09)  
D4: WO 01/47922 A (AVENTIS PHARMA LIMITED; COX, PAUL, JOSEPH; MAJID, TAHIR, NADEEM; LAI,) 5 July 2001 (2001-07-05)  
D5: MATASSA V G ET AL: "Evolution of a Series of Peptidoleukotriene Antagonists: Synthesis and Structure/Activity Relationships of 1,3,5-Substituted Indoles and Indazoles" JOURNAL OF MEDICINAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY. WASHINGTON, US, vol. 6, no. 33, 1990, pages 1781-1790, XP002077392 ISSN: 0022-2623  
D6: WO 03/101961 A (ASTRAZENECA AB; BONNERT, ROGER; BROUH, STEPHEN; COOK, TONY; DICKINSON) 11 December 2003 (2003-12-11)  
D7: WO 03/097598 A (SHIONOGI & CO., LTD; TANIMOTO, NORIHIKO; HIRAMATSU, YOSHIHARU; MITSUMO) 27 November 2003 (2003-11-27)  
D8: HOWARD H R ET AL: "SYNTHESIS AND ALDOSE REDUCTASE INHIBITORY ACTIVITY OF SUBSTITUTED 2(1H)-BENZIMIDAZOLONE- AND OXINDOLE-1-ACETIC ACIDS" EUROPEAN JOURNAL OF MEDICINAL CHEMISTRY, EDITIONS SCIENTIFIQUE ELSEVIER, PARIS, FR, vol. 27, no. 8, November 1992 (1992-11), pages 779-789, XP000981341 ISSN: 0223-5234  
D9: EP-A-0 254 241 (YOSHITOMI PHARMACEUTICAL INDUSTRIES, LTD) 27 January 1988 (1988-01-27)

2. Documents D6 and D7 are not taken into account in the present opinion, since they have been published after the priority of the present application.

3. **Novelty**

The compound s6h, 6i, 6l-n, 6r,15a-g disclosed in D8 and the compound disclosed in example 64 of D9 fall within the definition of formula (I) in claim 1 of the current

application. Novelty is not acknowledged re D8 and D9.  
The compounds disclosed in D1 to D3 have been excluded from the claimed matter  
by means of a proviso.

**4. Inventive step**

The problem underlying the present application appears to reside in the provision of indole, indazole or benzimidazole derivatives useful in the treatment of respiratory disorders in view of their activity on the prostaglandin D2 receptor. The same activity is disclosed for the compounds disclosed in D1 to D3. The structural difference compared to the current application resides in the fact that in D1 to D3 the carbon atoms of the benzo fused ring cannot be replaced by nitrogen atoms, while in the present application, it is mandatory that such a replacement takes place if ortho to the nitrogen of the indole a carbon atom is present, as defined in the proviso. D4 and D5 also describe compounds useful in the treatment of asthma; D4 discloses pyrrolo-pyridine and pyrrolo-pyrazine compounds, and thus teaches that the presence of nitrogen atoms in the ring fused to the pyrrolo does not affect the activity, while D5 indicates that the 5-membered ring may be additional contain a further nitrogen atom and that the acetic acid group may be attached to a nitrogen of the 5-membered ring. Since the skilled person would have arrived at the compounds of the present application by carrying out bioisosteric replacements in the structure of the known active compounds against asthma, no inventive step can be acknowledged in the absence of data which show unexpected effects for the compounds of the current application compared to the structurally closest compounds of the cited prior art.

**5. Industrial application**

Claims 11 and 12 are directed to a method for treatment of the human body by therapy.

**6. Further observations:**

- Claim 1 does not appear to mention the definition of X.